FDA Briefing Document

Oncologic Drugs Advisory Committee Meeting

October 5, 2009

NDA 022-465

VOTRIENT™ (pazopanib) Tablets

Applicant: GlaxoSmithKline

Proposed Indication: VOTRIENT™ is indicated for the treatment of patients with advanced renal cell carcinoma.

Table of Contents

I. BACKGROUND INFORMATION 4

II. REGULATORY HISTORY FOR PAZOPANIB 6

III. EFFICACY OF PAZOPANIB IN RCC 7

STUDY VEG105192 (KEY STUDY) 7
Results of Study VEG105192 8
STUDY VEG102616 (SUPPORTIVE) 13
STUDY VEG107769 (SUPPORTIVE) 14

IV. SAFETY PROFILE OF PAZOPANIB 15

OVERALL SAFETY OF PAZOPANIB IN THE RCC PROGRAM 15
SAFETY OF PAZOPANIB IN VEG105192 16
HEPATIC SAFETY OF PAZOPANIB 19
Excess and Marked ALT Elevations with Pazopanib Compared with Placebo 19
Presence of Hy's Law Cases 20
Observation of Hepatic Failure-Associated Deaths in the Pazopanib Clinical Program 22

V. CONCERNS ABOUT THE HEPATIC SAFETY OF PAZOPANIB 23

VI. SUMMARY 25

APPENDIX A (KEY INFORMATION ON DEATHS ASSOCIATED WITH OR RELATED TO HEPATIC FAILURE) 26

APPENDIX B 29

Table of Tables

Table 1: FDA-Approved Targeted Therapy for Treatment of Renal Cell Carcinoma 5
Table 2: Clinical Studies in RCC 7
Table 3: Geographic Distribution of the Patients 8
Table 4: Patient Demographics 9
Table 5: Baseline Disease Characteristics 9
Table 6: Patient Disposition 10
Table 7: Primary Endpoint Analysis Results by Independent Assessment 10
Table 8: Overall Response Rates in VEG105192 13
Table 9: Overall Response Rates in Study VEG102616 14
Table 10: Common Toxicities Observed in Pazopanib RCC Studies 15
Table 11: Overview of Adverse Events in VEG105192 16
Table 12: Deaths in VEG105192 16
Table 13: Common Adverse Events in VEG105192 17
Table 14: Important Adverse Events in VEG105192 17
Table 15: Common Laboratory Abnormalities in VEG105192 18
Table 16: Abnormalities of Transaminases and Bilirubin in VEG105192 19
Table 17: Differences in ALT and Bilirubin between Patients with and without Hepatic Metastases in the Pazopanib Arm of VEG105192 19
Table 18: Hepatic Laboratory Abnormalities in the Key Randomized Studies Supporting the Three Tyrosine Kinase Inhibitors for the Treatment of RCC 24

Table of Figures

Figure 1: Schema for Study VEG105192 8
Figure 2: K-M Curves for PFS Based on the Assessments by Independent Review 11
Figure 3: PFS Results of Subgroup Analyses 11
Figure 4: K-M Curves for Overall Survival (An Interim Analysis) 12
Figure 5: Time-Course of Hepatic Function Tests in Relation with Pazopanib 21
Figure 6 : Time-Course of Hepatic Function Tests in Relation with Pazopanib 21
Figure 7: Time-Course of Hepatic Function Tests in Relation with Pazopanib 22

I. Background Information

Pazopanib is a new tyrosine kinase inhibitor that targets vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor (PDGFR)-α and-β, and c-kit tyrosine kinases. It has been developed clinically as an antiangiogenic agent by GlaxoSmithKline (GSK) for the treatment of a variety of malignancies. In this NDA, GSK requests marketing approval of pazopanib for the treatment of advanced renal cell carcinoma (RCC).

The antitumor activity of pazopanib in RCC was observed in the early clinical studies. This prompted the sponsor to conduct a Phase 3 study, outside the U.S., comparing pazopanib with placebo in patients with advanced RCC. The Phase 3 study was initiated in April 2006, approximately 4 months after the approvals of sunitinib and sorafenib for the treatment of RCC. The results of this Phase 3 study constitute the key evidence supporting pazopanib in this NDA.

Since 2005, five targeted products have received FDA approval for the treatment of advanced RCC. Table 1 summarizes these products with their demonstrated efficacy in the key studies supporting their approval.

Table 1: FDA-Approved Targeted Therapy for Treatment of Renal Cell Carcinoma

Product Name* Approval	Trial Type/ Patient Population	Primary Endpoint	Key Findings
Sorafenib December 2005 Regular Approval	Randomized, double-blind comparison to placebo in patients with advanced RCC after one systemic therapy	PFS	HR: 0.44 (0.35-0.55) Median PFS 167 days vs. 84 days with placebo
Sunitinib January 2006 Accelerated Approval	Two single arm Phase 2 studies in patients with cytokine-refractory RCC	RR	34.0%; 36.5%
February 2007 Regular Approval	Randomized, double-blind comparison to IFNα in patients with treatment-naive advanced RCC	PFS	HR: 0.42 (0.32-0.54) Median PFS 47 weeks vs. 22 weeks with IFNα
Temsirolimus May 2007 Regular Approval	Randomized, open-label comparison to IFNα, in treatment-naive patients with advanced RCC with ≥3 of the 6 negative prognostic risk factors	OS	HR: 0.73 (0.58-0.92) Median OS 10.9 months vs. 7.3 months with IFNα
Everolimus March 2009 Regular Approval	Randomized, double-blind comparison to placebo in patients with RCC whose disease progressed after treatment with sorafenib, sunitinib, or both	PFS	HR: 0.33 (0.25-0.43) Median PFS 4.9 months vs. 1.9 months with placebo
Bevacizumab July 2009 Regular Approval	Randomized, double-blind comparison of bevacizumab + IFNα to IFNα alone in patients with RCC post-nephrectomy	PFS	HR: 0.60 (0.49-0.72) Median PFS 10.2 months vs. 5.4 months with IFNα alone

*All the products received regular approval except for sunitinib, which received accelerated approval in December 2006, followed by the conversion to regular approval in February 2007.
PFS: Progression-free survival; RR: Response rate; OS: Overall survival

II. Regulatory History for Pazopanib

GSK initiated the clinical development of pazopanib in September 2002 under IND 65,747. The regulatory history relevant to the proposed indication is summarized below.

- An end-of-Phase 1 meeting was held on July 28, 2005 to discuss the use of pazopanib in patients with metastatic or locally advanced RCC. At that time, the Agency stated, "If other drugs are approved and marketed to this population of patients at the time you start your study, a placebo controlled trial may be unethical and you may not be able to accrue patients." The Agency also stated, "The acceptability of PFS as an endpoint for approval depends on the magnitude of the difference, risk benefit ratio and whether any drugs are approved based on survival."

- A request for Special Protocol Assessment for Study VEG105192 was submitted on September 16, 2005 and a non-agreement letter was sent on November 3, 2005. The applicant submitted a complete response to the Special Protocol Assessment non-agreement letter on February 3, 2006. No agreement letter was issued in response to the revised protocol.

- A Type A meeting was held on March 10, 2006 to discuss the applicant's plan to enroll a treatment-naïve patient population outside of the U.S. where recently approved drugs were not available. The Agency stated, "Control patients with no prior therapy should receive either sorafenib, sunitinib, or a cytokine. The use of placebo in a second line patient population will be problematic unless patients have received one of these drugs." No agreement was reached on this protocol amendment.

III. Efficacy of Pazopanib in RCC

The three clinical studies that support the proposed indication for the treatment of advanced RCC are listed in Table 2.

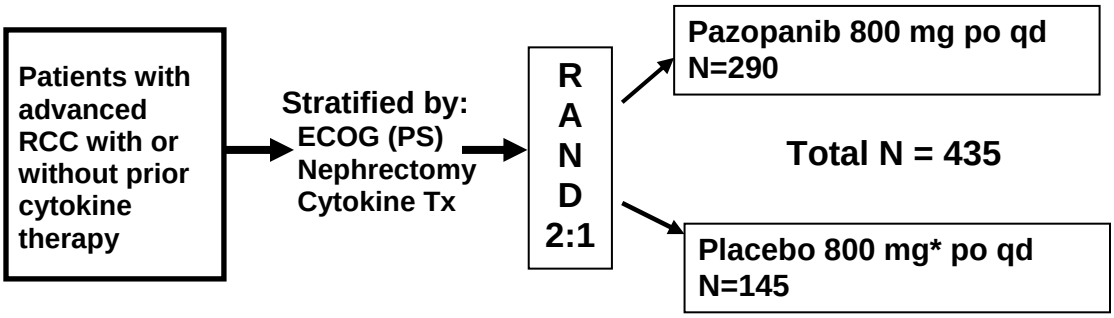
Table 2: Clinical Studies in RCC

Study Number	Study Design	Primary Endpoint	Dose Group	Status at Submission
VEG105192 (Key Study)	Randomized, double-blind, placebo-controlled, Phase 3 (N=435)	Progression-free survival	Pazopanib 800 mg vs. Placebo, once daily	Complete (120–day safety update submitted; follow-up for survival)
VEG102616 (Supportive)	Double-blind, placebo-controlled, randomized discontinuation design (Revised to single arm after the initial phase) (N=225)	Response Rate	Pazopanib 800 mg vs. Placebo (Revised from a discontinuation design to single arm pazopanib 800 mg after the first 60 patients)	Primary analysis complete (follow-up for safety)
VEG107769 (Supportive)	An extension single-arm study of patients (placebo) previously enrolled in VEG105192 (N=71)	Safety Evaluation	Pazopanib 800 mg	Primary analysis complete (study ongoing)

Study VEG105192 (Key Study)

VEG105192 was a Phase 3, randomized, double-blind, placebo-controlled multi-center study of pazopanib compared to placebo in patients with locally advanced and/or metastatic renal cell carcinoma who had received either one or no prior systemic cytokine (IL-2 or INFα) based therapy. Clear cell or predominantly clear cell RCC histology was required for study entry. Patients with no prior therapy were eligible for the study only if they were from countries or regions where no standard first-line therapy was available or where systemic cytokine therapy was not recognized as standard therapy for RCC. Eligible patients were stratified and randomized in a 2:1 ratio to receive either pazopanib or placebo as shown in Fig 1. Treatment continued until patients experienced disease progression, death, or unacceptable toxicity. Efficacy assessment was conducted every 6 weeks and then every 8 weeks after the first 24 weeks.

Figure 1: Schema for Study VEG105192



** Placebo tablets matching the pazopanib tablets*

The primary objective of the study was to evaluate and compare PFS between the two treatment arms. PFS was defined as the time from randomization to the time of documentation of disease progression or death due to any cause, as evaluated by an independent review committee (IRC). Disease progression was based on radiographic assessments of target and non-target lesions using the RECIST criteria. In the analysis of PFS, the interval between the date of randomization and the date associated with the last adequate assessment was used for patients who were alive without documented progression, discontinued due to toxicity, had extensive missing visits (12 weeks or more), or who received a new anticancer treatment without documented progression.

Major secondary endpoints included overall survival and overall response rate [complete response (CR) + partial response (PR)]. Overall survival was the principal secondary endpoint, defined as the time from randomization to death due to any cause. Patients who were alive at the time of the analysis were censored at the date of last contact. Response rate was defined as the percentage of patients achieving either a complete or partial tumor response per RECIST criteria.

All efficacy analyses for the endpoints described above were based on the Intent-to-Treat (ITT) population, which was comprised of all randomized patients.

Results of Study VEG105192

Study Accrual, Patient Baseline Demographics and Disease Characteristics

All 435 patients were from outside the United States, with the majority from Eastern Europe and Russia, as shown in Table 3.

Table 3: Geographic Distribution of the Patients

Geographic Region	Placebo N = 145	Pazopanib N = 290	Total N=435 (%)
Eastern Europe-Russia	69	146	215 (49%)
Western Europe	25	54	79 (18%)
South America	21	36	57 (13%)
Eastern Asia-Australia	21	35	56 (13%)
Western Asia	9	19	28 (7%)

Baseline demographics, as summarized in Table 4, were generally balanced between the treatment arms. The median age and male predominance are consistent with the disease demographics reported in the literature.

Table 4: Patient Demographics

Parameter	**Placebo N = 145**	**Pazopanib N = 290**
Sex		
Male, n (%)	109 (75%)	198 (68%)
Female	36 (25%)	92 (32%)
Age		
Median (range)	60 years (25-81)	59 years (28-85)
Race		
Caucasian	122 (84%)	252 (87%)
Asian	23 (16%)	36 (12%)
Other	0	2 (1%)
Performance Status		
0	60 (41%)	123 (42%)
1	85 (59%)	167 (58%)

Table 5 shows the patient baseline disease characteristics. Most patients had undergone prior nephrectomy and slightly more than half had received no prior cytokine-based systemic therapy. Few patients in either group were in the MSKCC poor risk category.

Table 5: Baseline Disease Characteristics

Parameter	**Placebo N = 145**	**Pazopanib N = 290**
Histology		
Clear Cell	129 (89%)	264 (91%)
Predominately Clear Cell	16 (11%)	25 (9%)
Prior Surgery		
Nephrectomy	127 (88%)	258 (89%)
Other	14 (10%)	20 (7%)
Prior Therapy		
Cytokine	67 (46%)	135 (47%)
None (treatment-naïve)	78 (54%)	155 (53%)
MSKCC Risk Factors*		
0 (Favorable)	57 (39%)	113 (39%)
1-2 (Intermediate)	77 (53%)	159 (55%)
≥3 (Poor)	5 (3%)	9 (3%)
* The 5 risk factors are a poor performance status (<80%), a low serum hemoglobin level, an elevated serum LDH level, an elevated corrected serum calcium, and a time interval of <1 year from diagnosis to treatment.		

The majority of patients discontinued treatment with either pazopanib or placebo at the time of clinical cut-off due to the reasons as shown in Table 6. Discontinuation due to an Adverse Event, Withdrawal, or Other will be discussed below.

Table 6: Patient Disposition

	Placebo N = 145	**Pazopanib N = 290**
Enrolled	145	290
Treated		
On Treatment	14 (10%)	63 (22%)
Off Treatment*	131 (90%)	227 (78%)
Progressive Disease	112	147
Death	9	11
Adverse Events	5	41
Lost to Follow Up	1	3
Withdrawal	2	14
Other	2	11
*Reasons for study discontinuation were based on investigator's assessments.		

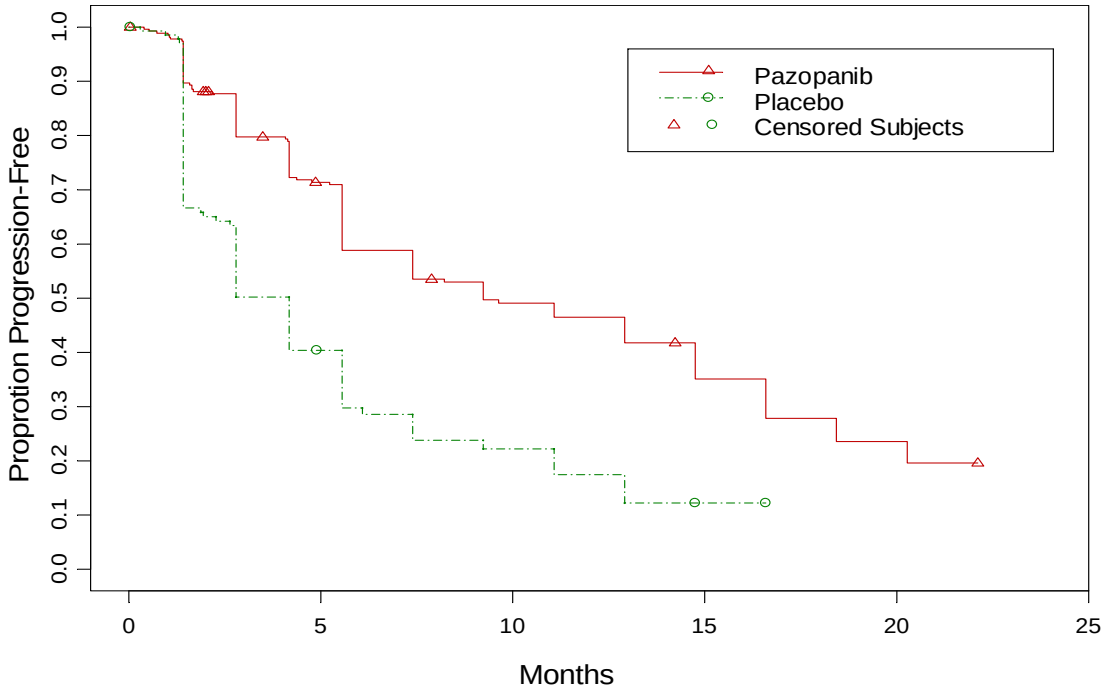
Efficacy Results of VEG105192

The primary analysis is shown in Table 7 and Figure 2. The primary endpoint, PFS, was based on independent, blinded assessments of disease progression. The primary analysis was conducted in the intent-to-treat population. The median PFS in patients treated with pazopanib was 9.2 months as compared to a median PFS of 4.2 months in patients receiving placebo (HR 0.46, $p<0.0000001$). The PFS results remained consistent in subgroup analyses, as shown in Fig. 3. Several sensitivity analyses of PFS also revealed consistent results.

Table 7: Primary Endpoint Analysis Results by Independent Assessment

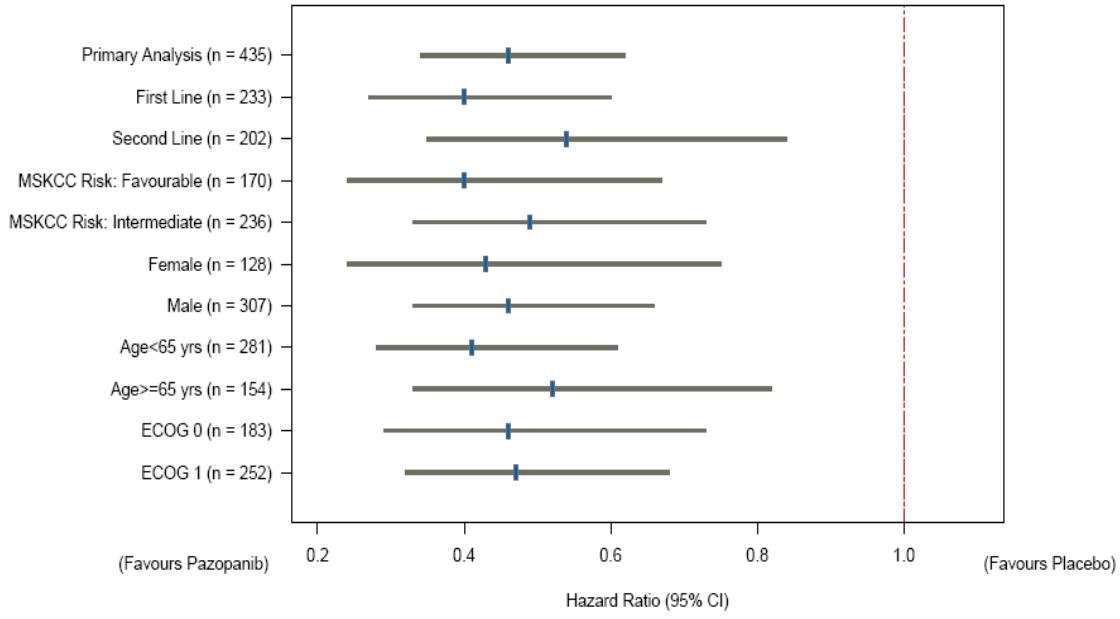
	Placebo N = 145	**Pazopanib N = 290**
Status		
Progressed or Died	98 (68%)	148 (51%)
Censored	47 (32%)	142 (49%)
Progression Free Survival		
Median (95% CI)	4.2 mo (2.8, 4.2)	9.2 mo (7.4, 12.9)
Adjusted Hazard Ratio (95% CI)	0.46 (0.34, 0.62)	
Stratified Log-rank p value	< 0.0000001	

Figure 2: K-M Curves for PFS Based on the Assessments by Independent Review



The following figure shows PFS results from subgroup analyses. Note that treatment-naïve patients seemed to benefit more than patients who had received prior cytokine therapy, but that the confidence intervals overlap.

Figure 3: PFS Results of Subgroup Analyses



PFS differences by region were also analyzed. For patients in the Eastern Europe-Russia region (49% of 435 patients), the median PFS for patients treated with pazopanib was 7.39 months as compared to a median PFS of 4.17 months in patients receiving placebo [HR 0.46 with 95% C.I. (0.32, 0.67)]. For patients not in the Eastern Europe-Russia region, the median PFS for patients treated with pazopanib was 12.91 months as compared to a median PFS of 2.79 months in patients receiving placebo [HR 0.42 with 95% C.I. (0.29, 0.61)]. While both groups appeared to benefit from pazopanib, the PFS of patients treated with pazopanib in Eastern Europe-Russia was markedly worse than those treated in other parts of the world. However, the patients in placebo arm in Eastern Europe-Russia appeared to do slightly better than those treated in other parts of the world. The reasons for this difference are unclear.

Per the sponsor's statistical analysis plan, an interim OS analysis was planed at the time of the final PFS analysis. The interim analysis showed that there was no statistically significant difference in OS. The hazard ratio for overall survival was 0.73 (95% CI: 0.53 - 1.00) with a one-sided p-value of 0.02 (>0.004, significance level allocated for the interim OS analysis). At the time of analysis, 176 deaths (61%) of the required events (287 deaths) had occurred. However, since 70 patients from the placebo arm had crossed over to receive pazopanib in the extension study at the time of the interim analysis, longer follow up may not demonstrate a statistically significant difference in overall survival. The final OS analysis will be conducted when 287 deaths have occurred. The Kaplan-Meier curves for overall survival are shown in Fig 4. The other key secondary endpoint, overall response rate, is shown in Table 8.

Figure 4: K-M Curves for Overall Survival (An Interim Analysis)

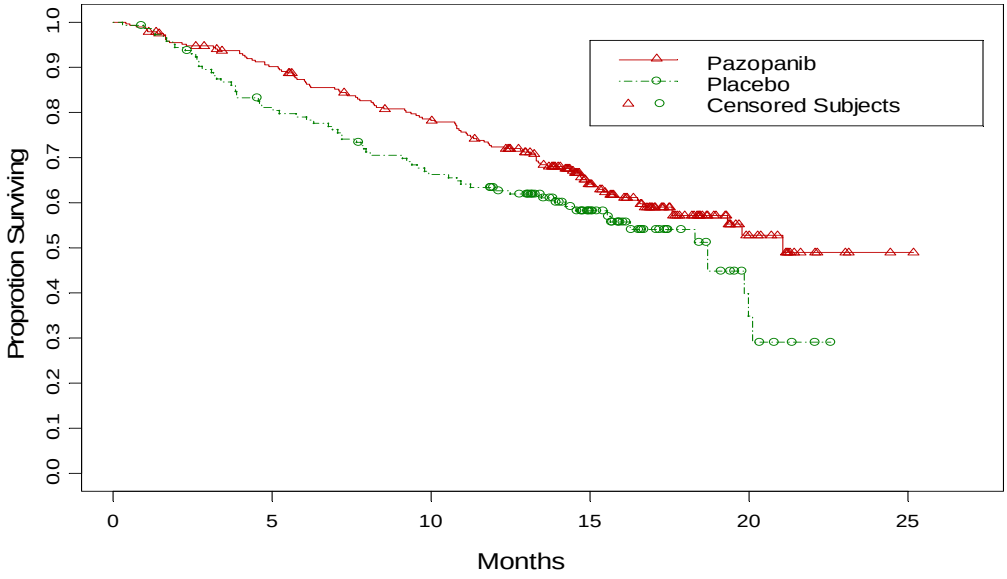


Table 8: Overall Response Rates in VEG105192

	Placebo N=145	**Pazopanib N=290**
Overall RR (CR+PR) N (%) (95% CI)	5 (3%) (0.5%, 6.4%)	88 (30%) (25.1%, 35.6%)
CR: N (%)	0 (0%)	1 (<1%)
PR: N (%)	5 (3%)	87 (30%)
Duration of Response Median (95% CI)	--*	58.7 weeks (52.1, 68.1)
RR in Treatment- Naïve Group (95% CI)	4% (0, 8.1%)	32% (24.3%, 38.9%)
RR in Cytokine Pretreated Group (95% CI)	3% (0, 7.1%)	29% (21.2%, 36.5%)

*The number of patients is too small to provide a meaningful estimate of the duration of response.

Study VEG102616 (Supportive)

VEG102616 was a phase 2 study of oral pazopanib 800 mg once daily in patients with advanced RCC who had failed only one prior systemic therapy or who had received no prior therapy. The primary objective was to assess the antitumor activity of pazopanib in RCC and to determine the overall response rate (CR + PR) in the study patient population. The study was initially designed as a randomized discontinuation study; however, it was amended to an open-label treatment study after a planned interim analysis of the rate of stable disease in the first 60 enrolled patients suggested that pazopanib was "highly active" in the disease.

A total of 225 patients recruited from 9 countries were enrolled in the study. Sixty-three of them (28%) were from the United States. The median age of the study population was 60 years old and the majority of patients were Caucasian. Approximately 69% of the patients had not received systemic therapy.

Response rates by independent review are summarized in Table 9. Note that response rate, in the Phase 3 study above and in this Phase 2 trial, does not appear to be affected by prior cytokine therapy.

Table 9: Overall Response Rates in Study VEG102616

	Number of Responses (%)
Response Rate in All Patients	**N = 225**
ORR (CR + PR) N (%)	78 (34.7%)
CR: N (%)	3 (1.3%)
PR: N (%)	75 (33.3%)
Response Rate in Treatment-Naïve Patients	**N = 155**
ORR (CR + PR) N (%)	52 (33.5%)
CR: N (%)	2 (1.3%)
PR: N (%)	50 (32.3%)
Response Rate in Pre-Treated Patients	**N = 70**
ORR (CR + PR) N (%)	26 (37.1%)
CR: N (%)	1 (1.4%)
PR: N (%)	25 (35.7%)

Study VEG107769 (Supportive)

VEG107769 was an open-label extension study of VEG105195, initiated in September 2006. It allowed patients who were initially randomized in the placebo arm to receive pazopanib at the time of disease progression. The rationale for the unilateral cross-over was based on both emerging clinical data from other products similar to pazopanib showing clinical benefits in the studied disease and the known safety profile of pazopanib at the time of study initiation. The primary objective was to evaluate the safety and tolerability of pazopanib at the 800 mg daily dosing schedule. The first secondary objective was to evaluate overall response rate.

A total of 71 of the 145 patients initially enrolled on the placebo arm were enrolled in this study. One of these patients was from the pazopanib arm of VEG105192 because of an investigator's request. The safety profile of pazopanib from this study will be evaluated in the next section together with the information from the other studies in RCC.

The investigator assessed overall response rate was 32.4% (CR 0 + PR 32.4%), consistent with the response rates observed in the other two RCC studies as discussed above.

IV. Safety Profile of Pazopanib

The evaluation of the safety of pazopanib was mainly based on the data from the three studies in the RCC program, with a focus primarily on the Phase 3, placebo-controlled study VEG105192. Safety signals from the RCC program or safety concerns raised by products similar to pazopanib were also examined in the non-RCC, pazopanib monotherapy studies that have evaluable data (N=397).

Overall Safety of Pazopanib in the RCC Program

The three RCC studies had 593 patients who received at least one dose of pazopanib. The median duration of exposure was 7.7 months (range 0.1-38.6). Adverse events (AEs) were reported in 566 (95%) of the 593 patients, with 21 (4%) fatal serious adverse events (SAEs) during the studies. The fatal SAEs occurring in 2 or more patients included hemorrhage (6), cardiac or cardiovascular events (3), sudden death (3), colonic perforation (2) and hepatic failure (2).

The most commonly reported adverse events or reactions with a frequency of >20% and the most commonly detected laboratory abnormalities are listed in Table 10.

Table 10: Common Toxicities Observed in Pazopanib RCC Studies

Clinical Parameter	**Pazopanib N=593**		
	All Grades	**Grade 3**	**Grade 4**
Adverse Event			
Diarrhea	55%	4%	<1%
Hypertension	41%	6%	0
Hair Color Change	40%	<1%	0
Nausea	32%	<1%	0
Fatigue	29%	4%	0
Anorexia	24%	2%	0
Vomiting	21%	2%	<1%
Laboratory Test			
ALT	52%	9%	1%
AST	54%	6%	<1%
Hyperglycemia	48%	2%	0
Bilirubin (total)	36%	2%	<1%
Hypophosphatemia	36%	4%	0
Hyponatremia	35%	6%	<1%
Increase in Creatinine	29%	0	<1%
Alk Phosphatase Increase	27%	2%	<1%
Hyperkalemia	27%	5%	<1%

Safety of Pazopanib in VEG105192

In VEG105192, the median duration of exposure to pazopanib was 7.4 months (0.3-23.1) as compared to the median duration of exposure to placebo, 3.8 months (0.3-22.0). The adverse event profile of the two arms is summarized in Table 11.

Note that the percentage of patients experiencing any adverse event, an adverse event leading to discontinuation and a serious or fatal adverse event was higher in the pazopanib arm. The primary adverse event leading to discontinuation of pazopanib was abnormal hepatic function tests, occurring in 11 of 46 patients. Additional adverse events that caused discontinuation of pazopanib in > 2 patients included cardiovascular events (myocardial infarction, ischemic cerebral stroke, or transient ischemic attack) in 6 patients, fatigue in 4 patients, gastrointestinal disturbance in 4 patients, and proteinuria in 3 patients. No adverse events in the placebo arm caused treatment discontinuation in 2 or more patients.

Nine and 10% of patient in each arm died within 28 days after the last dose of study drug, as shown in Table 12; whereas few patients died within 28 days after first receipt of study drug. The primary cause of death during study was disease progression. However, 4 patients in the placebo arm and 13 in the pazopanib arm experienced a fatal adverse event. Fatal adverse events included bleeding (4), cardiac/cardiovascular events (3), hepatic failure (1) and sudden death (1), GI perforation (1), and other (3).

Table 11: Overview of Adverse Events in VEG105192

	Placebo N=145	**Pazopanib N=290**
All AEs (%)	107 (74%)	271 (93%)
AEs Leading to Discontinuation	7 (5%)	46 (16%)
SAEs (%) Fatal SAEs	28 (20%) 4 (3%)	74 (26%) 13 (4%)

Table 12: Deaths in VEG105192

	Placebo N=145	**Pazopanib N=290**
Death (%)	76 (52%)	147 (51%)
≤28 days from First Dose	1 (<1%)	3 (1%)
≤28 days from Last Dose	13 (9%)	31 (10%)
>28 days from Last Dose	62 (43%)	113 (39%)
Cause of Death		
Disease Progression	66 (46%)	127 (44%)
Cardiovascular	1	5
Sudden Death	2	2
Bleeding	0	4
Hepatic	1	1
Other *	6	8

*included infections, pulmonary edema, gastrointestinal perforation, and unknown or unspecified.

The commonly reported adverse events with a frequency of ≥20% in the pazopanib arm are shown in Table 13. Their incidence rates in the pazopanib arm appear consistent with those in the overall RCC program, but are higher than the corresponding rates observed in the placebo arm.

Table 13: Common Adverse Events in VEG105192

Adverse Event	Placebo N=145		Pazopanib N=290	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Diarrhea	13 (9%)	1 (<1%)	152 (52%)	13 (5%)
Hypertension	16 (11%)	1 (<1%)	116 (40%)	14 (5%)
Hair Color Change	5 (3%)	0	109 (38%)	1 (<1%)
Nausea/Vomiting	23 (16%)	3 (2%)	104 (36%)	8 (3%)
Abdominal Pain/Discomfort	12 (9%)	2 (1%)	63 (21%)	9 (3%)
Fatigue	13 (9%)	4 (2%)	57 (20%)	7 (2%)

Selected clinically important adverse events in VEG105192 are listed in Table 14. These events were examined since they have been recognized in association with other vascular endothelial growth factor inhibitors. As shown, a disproportionate number of patients in the pazopanib arm developed arterial ischemia (in the coronary arteries or in other major arteries) as compared to the placebo arm. The incidence of other listed adverse events was also greater in the pazopanib arm than in the placebo arm.

Table 14: Important Adverse Events in VEG105192

Adverse Event	Placebo N=145		Pazopanib N=290	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Hemorrhage	8 (6%)	0	32 (11%)	7 (2%)
Myocardial Infarction/Ischemia	0	0	8 (3%)	6 (2%)
Stroke/TIA	0	0	5 (2%)	3 (1%)
Venous Thrombosis*	2 (1%)	1 (<1%)	3 (1%)	2 (1%)
Fistula/Perforation	0	0	3 (1%)	2 (1%)
Hand-Foot Syndrome	1 (<1%)	0	16 (6%)	2 (1%)
Proteinuria	0	0	29 (10%)	6 (2%)
*Includes vena cava thrombosis, renal vein thrombosis, and splenic vein thrombosis.				

The effect of pazopanib on the QTc interval and on the development of arrhythmias was also examined. Among 479 patients with renal cell carcinoma with an EKG who were treated with pazopanib, 11 (2.3%) had a QTc $\geq$ 500 msec. Arrhythmias were not reported in any of these patients. However, one patient on the pazopanib arm of VEG105192 developed cardiac arrest associated with torsades and one patient on VEG102616 developed ventricular fibrillation associated with torsades 7 days after discontinuation of study drug.

Declines in left ventricular ejection fraction (LVEF) have been reported with other tyrosine kinase inhibitors. In the RCC studies, monitoring of LVEF was not performed during the study since the preclinical and early clinical studies did not suggest that a decline LVEF is an important safety signal for pazopanib. Recently, changes in LVEF were monitored in a Phase 2 study of 1) pazopanib, 2) lapatinib, and 3) pazopanib plus lapatinib in patients with advanced cervical cancer (Study VEG105281). LVEF was measured at baseline, week 3, and then every 9 weeks. With a median treatment exposure of 2.9 months (0.2-15.3) in the 74 patients receiving pazopanib alone, no patients had a LVEF <40%. However, one patient had a 10% decrease in LVEF to a level below the institute lower limit of normal.

Laboratory Results

The common laboratory abnormalities are shown in Table 15. The remarkable laboratory difference between the two arms is the frequency of Grade 3/4 elevations in ALT/AST, 14% in the pazopanib arm compared to 1% with placebo. As such, hepatic toxicity was further reviewed and the important findings are reported in the next section.

Note that while the incidence of anemia was much higher in the pazopanib arm, the incidence of grade 3-4 events was similar between pazopanib and placebo. Likewise, the incidence of neutropenia and thrombocytopenia were increased in the pazopanib arm, but this was primarily due to Grade 1-2 events.

Table 15: Common Laboratory Abnormalities in VEG105192

Test	Placebo N=145			Pazopanib N=290		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
ALT/AST	47 (32%)	2 (1%)	0	195 (67%)	36 (12%)	5 (2%)
Hyponatremia	43 (30%)	8 (4%)	0	105 (36%)	14 (5%)	4 (2%)
Hypophosphatemia	24 (16%)	2 (1%)	0	103 (36%)	13 (5%)	0
Hypomagnesemia	37 (25%)	0	0	88 (30%)	2 (1%)	4 (2%)
Anemia	88 (26%)	2 (1%)	1 (<1%)	156 (55%)	5 (2%)	2 (1%)
Neutropenia	13 (9%)	0	0	105 (36%)	4 (2%)	1 (<1%)
Thrombocytopenia	13 (9%)	0	1 (<1%)	103 (35%)	4 (2%)	1 (<1%)

Hepatic Safety of Pazopanib

Excess and Marked ALT Elevations with Pazopanib Compared with Placebo

Since the incidence of serum aminotransfererase elevations in the pazopanib arm was considerably higher than that in the placebo arm, laboratory tests specific to hepatic injury were examined further and the results are shown in Table 16. ALT, which is more specific than AST for hepatocellular injury, was elevated more frequently with pazopanib than with placebo. The majority of the elevations occurred within the first 12 weeks of treatment. The rate of ≥ Grade 2 ALT elevation, defined as > 2.5xULN, was 23% in the pazopanib arm compared to 3% in the placebo arm; the rate of ≥ Grade 3 ALT elevation (defined as > 5.0xULN) was 13% in the pazopanib arm versus 1% in the placebo arm. As analyzed in Table 17, the high incidence of ALT elevation in the pazopanib arm does not appear to be related to the presence or absence of hepatic metastases. While the majority of these Grade 3 and 4 ALT elevations were found to be reversible with either dosing modifications (interruption and/or dose reduction) or treatment continuation with no dose modifications, two patients did have an irreversible ALT abnormality and did go on to hepatic failure. One had tumor involvement of the liver, the other one (Subject 386) is described in Appendix A.

Table 16: Abnormalities of Transaminases and Bilirubin in VEG105192

Test	Placebo N=145					Pazopanib N=290				
	All Grades	Grade 1	Grade 2	Grade 3	Grade 4	All Grades	Grade 1	Grade 2	Grade 3	Grade 4
ALT	37 (26%)	32 (22%)	3 (2%)	1 (1%)	0	172 (59%)	107 (37%)	29 (10%)	31 (11%)	5 (2%)
AST	31 (22%)	26 (18%)	4 (2%)	1 (1%)	0	168 (58%)	118 (41%)	27 (9%)	21 (7%)	2 (1%)
Bilirubin (total)	20 (14%)	13 (9%)	4 (2%)	2 (1%)	1 (1%)	108 (37%)	60 (20%)	39 (13%)	7 (2%)	2 (1%)
ALT elevations > 3xULN: 3% with placebo vs. 19% with pazopanib										

Table 17: Differences in ALT and Bilirubin between Patients with and without Hepatic Metastases in the Pazopanib Arm of VEG105192

Test	Pazopanib N=290									
	Patients with Hepatic Lesions* N=93					Patients without Hepatic Lesions** N=197				
	All Grades	Grade 1	Grade 2	Grade 3	Grade 4	All Grades	Grade 1	Grade 2	Grade 3	Grade 4
ALT	50 (54%)	34 (37%)	9 (10%)	5 (5%)	2 (2%)	122 (62%)	73 (37%)	20 (10%)	26 (13%)	3 (2%)
Bilirubin (total)	41 (44%)	26 (28%)	11 (12%)	3 (3%)	1 (1%)	67 (37%)	34 (17%)	28 (14%)	4 (2%)	1 (1%)

Based on the independent review of RCC lesions.
*Patients with any hepatic lesions (target, non-target, and new lesions) during study
**Including Subject 440 whose lesions were not documented in the independent review. The subject's baseline scans did not meet the protocol requirements.

Presence of Hy's Law Cases

Given the increased incidence of elevations in ALT and bilirubin with pazopanib, the database of both the RCC studies and the monotherapy non-RCC studies were examined for cases that would meet the definition of Hy's Law. Hy's Law is defined as a concurrent elevation in ALT > 3xULN and total bilirubin > 2xULN with no evidence of biliary obstruction or of other causes that can reasonably explain the elevation. Alkaline phosphatase should not be substantially elevated (e.g. a < 3 xULN elevation can be seen in almost any type of liver disease according to Harrison's Principles of Internal Medicine, 16th edition). Therefore, it is critical to rule out an obstructive basis for the elevated bilirubin and to rule out other causes of hepatic injury (e.g., liver metastases, other drugs or viral hepatitis) in defining a Hy's Law case. Medications which are able to cause an elevation in ALT (hepatic injury) along with a reduction in the synthesis and transportation of bilirubin (injury that interferes with normal liver function) are more likely to be associated with a significant risk of severe hepatotoxicity. After screening the pazopanib monotherapy population (N=990), four cases that met the Hy's Law criteria were identified. All four patients were from the RCC studies (N=593), three in VEG105192 and one in VEG107769. All had concurrent elevations of ALT > 3xULN and total bilirubin > 2xULN, but with either normal alkaline phosphatase or a value < 3xULN.

Figures 5-7 show the time course of the liver tests in three of the four patients (Patients 152, 170, 386, and 410) who met the Hy's Law criteria. The last patient is shown in Appendix A (Patient 386) since this patient's death, occurring 4 days after the onset of hyperbilirubinemia, was associated with fulminant hepatic failure. (Appendix A includes the narratives of three patients (Patients 121, 233, and 386) who died due to hepatic failure while receiving pazopanib). None of the four patients had evidence of other factors that could contribute to the hepatic abnormalities, such as liver metastases. Note that Patient 170 took both acetaminophen as needed (approximately 1600 mg daily) and pazopanib prior to the first elevation in ALT to > 3xULN and total biliurubin to > 2xULN. The abnormalities returned to normal levels after discontinuation of the two drugs. However, hepatocellular injury recurred within a week after the patient was rechallenged with pazopanib (at a 50% dose) in the absence of acetaminophen or other confounding factors. The patient developed icterus (no bilirubin levels were reported) and pazopanib was discontinued. Three weeks later, the patient died of hemoptysis. The hepatic toxicity remained unresolved at the time of death. No clinical information was available to verify if the hemoptysis was related to a potential coagulopathy secondary to the hepatotoxicity. In the other two patients, no confounding factors or reasons other than pazopanib were found to adequately explain the concurrent elevations of ALT and bilirubin. One (Patient 152) of the two patients had normal hepatic function 4 weeks after discontinuation of treatment, but the other patient (Patient 410) had resolution of the hepatic abnormalities while continuing treatment with no dose modification.

Figure 5: Time-Course of Hepatic Function Tests in Relation with Pazopanib

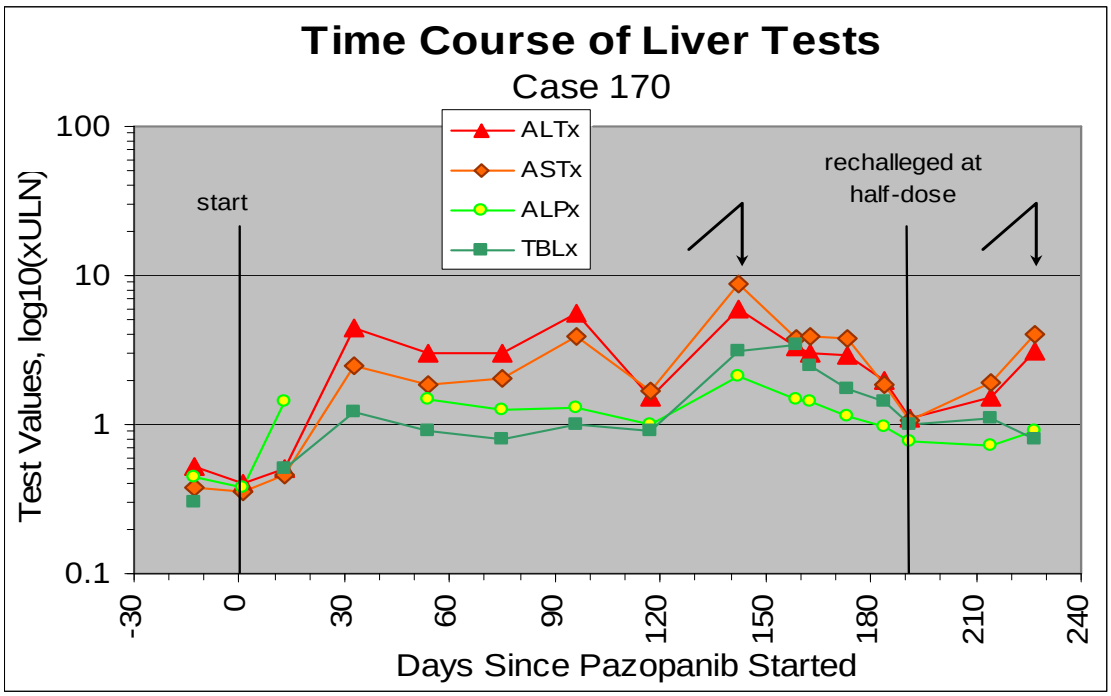


Figure 6 : Time-Course of Hepatic Function Tests in Relation with Pazopanib

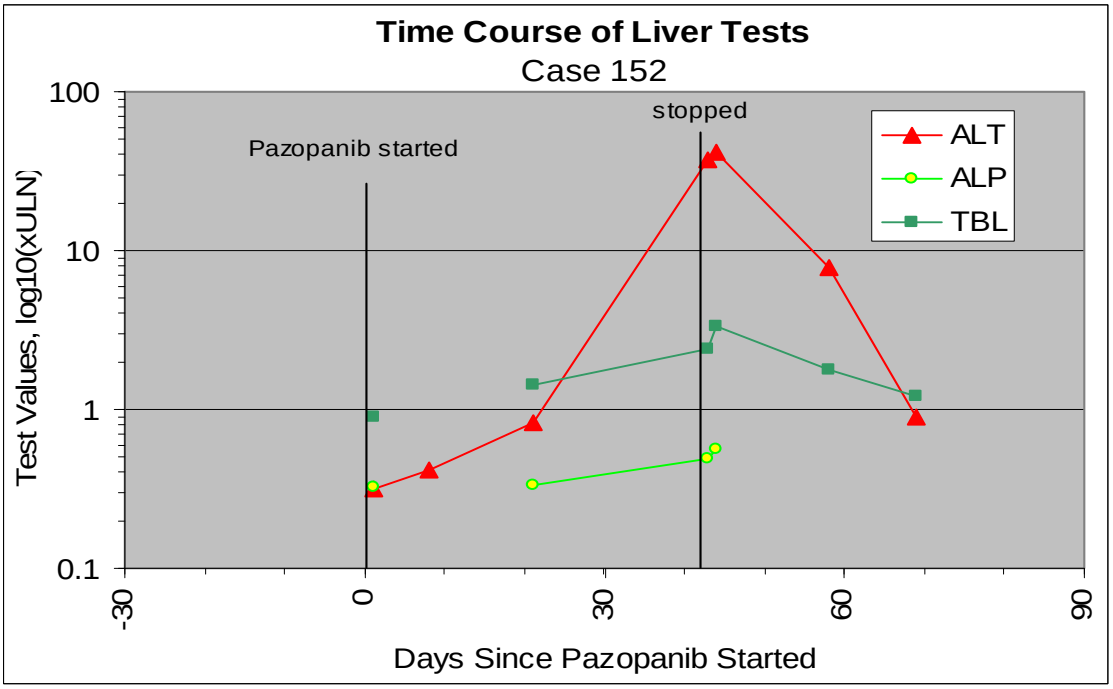
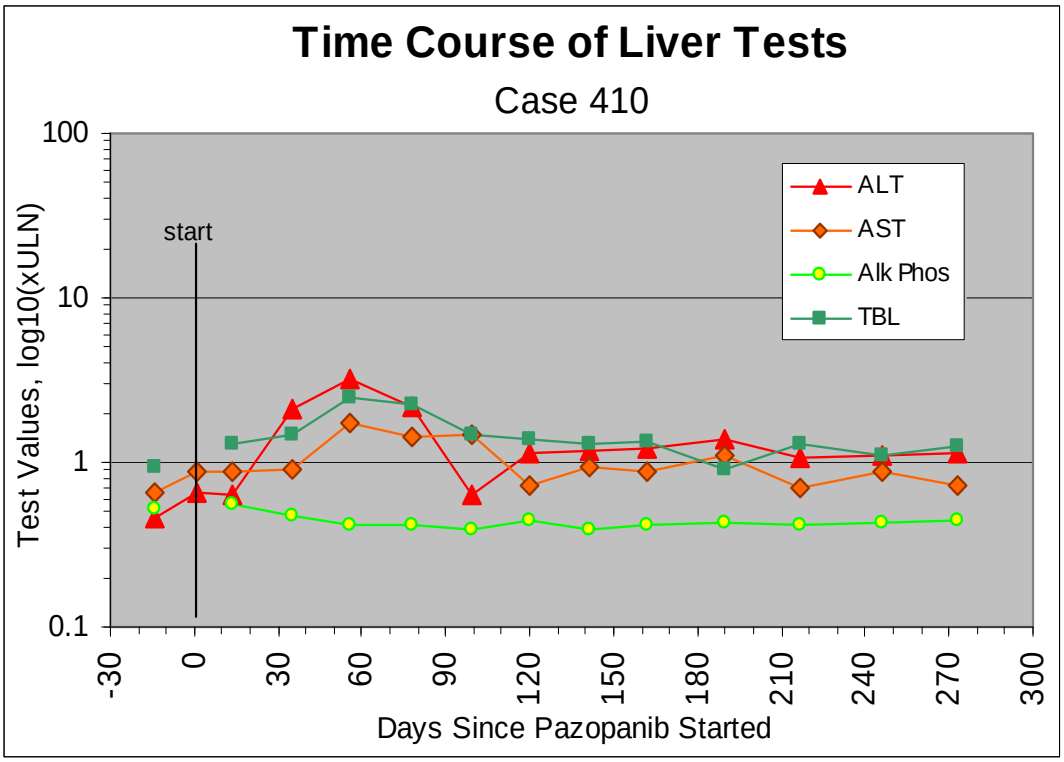


Figure 7: Time-Course of Hepatic Function Tests in Relation with Pazopanib



Observation of Hepatic Failure-Associated Deaths in the Pazopanib Clinical Program

Three deaths were associated with or likely related to hepatic injury in the clinical studies of pazopanib. Two cases were found in the RCC program (Patient 386 in VEG105192 and Patient 233 in VEG102616), and one was from a Phase 1 study of daily pazopanib in combination with two doses of topotecan on Days 1 and 15 only (Patient 121 in Study HYT109091). Key medical information on each case is provided in Appendix A. Patient 121 also met the criteria for Hy's Law. Although this case was not included in the Hy's Law analysis of the pazopanib monotherapy population as discussed above, Patient 121 actually received pazopanib monotherapy for 17 days prior to the detection of the hepatic abnormality. For this case, hepatic failure and subsequent death (one week after the detection of the hepatic abnormality) were considered probably related to pazopanib by the investigator, GSK, and FDA despite the GSK-proposed possibility of ischemic injury to the liver. For the other 2 cases in the RCC studies, the evidence found in their medical records and the datasets does not exclude the attribution of severe hepatotoxicity and subsequent death to pazopanib. The severe hepatoxicity in Patient 386 was considered possibly related to pazopanib by

both the investigator and FDA reviewers. One of many concerns in reviewing the three patients is the time course of their illness: the hepatotoxicity occurred within or around a month of beginning pazopanib and the patient quickly deteriorated and died within a week of the onset of the hepatotoxicity. The scheduled laboratory monitoring of hepatic function tests did not help them in avoiding the fatal hepatotoxicity. The clinical features demonstrated in the three patients suggest that the occurrence of pazopanib-associated fatal hepatoxicity is unpredictable.

Taken together, the evidence of hepatocellular injury revealed in the pazopanib application has the following features:

a) Pazopanib caused an excess incidence of ALT elevations > 3xULN compared to placebo (19% vs. 3%, a difference of 16%);

b) Marked ALT elevations (Grade 3/4) occurred with pazopanib, but not with placebo (13% vs. 1%);

c) Four patients in the pazopanib monotherapy population had concurrent elevation of total bilirubin > 2xULN and ALT > 3xULN with no evidence of biliary obstruction or other findings that adequately explain the bilirubin elevations; and

d) Three deaths have been associated with liver failure. One (a Hy's law case identified in a combination study) was considered probably related to pazopanib by the investigator, GSK, and FDA. The other two deaths did not have adequate clinical evidence to rule out the attribution of the death to pazopanib.

All these features suggest a significant risk of pazopanib-induced severe hepatic injury in a larger patient population in a post-marketing setting. Please see Guidance for Industry-Drug-Induced Liver Injury: Premarketing Clinical Evaluation (drafted in October, 2007, and finalized in July, 2009).

V. Concerns about the Hepatic Safety of Pazopanib

Pazopanib is the third tyrosine kinase inhibitor (TKI) submitted to FDA for marketing evaluation for the treatment of advanced renal cell carcinoma. It is difficult to compare the safety and efficacy of pazopanib with the two other TKIs that have received approval for the treatment of advanced renal cancer unless they are compared in randomized trials. GSK is currently conducting a Phase 3 study comparing pazopanib with sunitinib in patients with advanced RCC, but no results are available at present. Nevertheless, many adverse events or reactions such as gastrointestinal disturbances, bleeding, visceral perforation, increases in blood pressure and arterial thrombosis seem common to TKI inhibitors. In contrast, differences in adverse events may also exist among these inhibitors. One important difference is the incidence and severity of

hepatic toxicity. This is based on the controlled Phase 3 studies in their premarketing submissions, as summarized in Table 18. The rates shown here should not be compared directly to each other because of the inherent problems with cross study comparisons.

Table 18: Hepatic Laboratory Abnormalities in the Key Randomized Studies Supporting the Three Tyrosine Kinase Inhibitors for the Treatment of RCC

	The Sorafenib Study*		**The Sunitinib Study****		**The Pazopanib Study**	
	Sorafenib N=384	Placebo N=384	Sunitinib N=375	IFNα N=360	Pazopanib N=290	Placebo N=145
ALT						
Any Grade	24%	19%	46%	39%	59%	26%
Grade 3/4	0	<1%	3%	2%	**13%**	**<1%**
Bilirubin						
Any Grade	8%	6%	19%	2%	37%	14%
Grade 3/4	n/f	n/f	1%	0	3%	2%

*Based on the initial medical review of sorafenib for treatment of RCC, accessed through Drugs@fda.
** Based on the review of sunitinib for RCC, accessed through Drugs@fda.

Recent literature reports show a few cases of sorafenib- or sunitinib-associated hepatic failure and deaths after 3-4 years of marketing. This may be suggestive of a class effect of these tyrosine kinase inhibitors. Because of the voluntary nature of the reports, it is impossible to estimate the frequency and to reliably establish a causal relationship. However, in their premarketing submissions, there was no hepatic safety signals revealed during the reviews of both drugs. Two cases of hepatic failure associated death were described in the review of the sunitinib, with the conclusion that there was an equivocal suggestion of hepatoxicity caused by sunitinib despite known tumor involvement at baseline and a minimum increase in hepatic function tests. Overall, neither sunitinib nor sorafenib disclosed a significant hepatic safety signal in the pre-marketing evaluations.

The significance of the premarketing hepatic safety profile of pazopanib as demonstrated in the current application is different from that of the post-marketing safety information gathered on either sunitinib or sorafenib. As discussed above, this premarketing hepatic information may predict a significant risk of severe hepatic injury with pazopanib. Although the majority of the patients who had severe hepatocellular injury had resolution of the toxicities with dosing modifications, it is very important to recognize that, based on the three deaths described above, patients receiving pazopanib can develop irreversible, rapidly progressive fatal hepatoxicity that may not be prevented by close monitoring of hepatic function during treatment. Such risk could be justified if there were no effective therapies for the disease or if an improvement in

survival had been demonstrated. Given that the demonstrated efficacy of pazopanib in RCC appears to be similar to the other two drugs and that additional products are also available for the treatment of the disease, exposure of patients to the risk of severe and fatal hepatoxicity related to pazopanib is problematic.

Drugs possessing less hepatotoxicity than pazopanib in other settings (non-cancer therapeutic areas) have been withdrawn after being marketed because of fatal hepatic failure or did not receive regulatory approval due to their predicted risk of severe hepatoxicity. For reference only, Appendix B shows a few illustrative examples from the Guidance for Industry-Drug-Induced Liver Injury: Premarketing Clinical Evaluation (drafted in October, 2007, and finalized in July, 2009). It remains unclear if the hepatotoxicity guidelines used in making the regulatory decisions for these products are applicable to evaluation of the hepatotoxicity of an antitumor product such as pazopanib.

VI. Summary

In this NDA, pazopanib, a new tyrosine kinase inhibitor, is proposed for the treatment of patients with advanced renal cell carcinoma. The key evidence supporting the proposed indication is a randomized, placebo controlled Phase 3 trial of pazopanib in advanced RCC. The efficacy results of the study showed a 5-month improvement in median PFS [HR 0.46 (0.34-0.62), $p<0.0000001$], but without a statistically significant improvement in overall survival. The safety results, compared with placebo, showed an excess incidence of moderate to marked ALT elevations with pazopanib, in addition to the occurrence of important adverse reactions known to VEGF inhibitors, including hypertension, hemorrhage, arterial and venous thrombosis, gastrointestinal perforation, and proteinuria. Further, pazopanib has been associated with a prolonged QT interval and two cases of torsades de pointes.

With pazopanib monotherapy, a high incidence of hepatic laboratory abnormalities was associated with four cases that fulfilled Hy's Law (about 0.4%). More importantly, three hepatic deaths related to or associated with pazopanib were also observed in a premarketing setting. These hepatic findings strongly suggest that pazopanib may be associated with a significant risk of severe idiosyncratic hepatic injury if used in a larger patient population after marketing. As such, FDA is concerned about the benefit-to-risk ratio of pazopanib in the intended population of patients. This is particularly true in a setting in which there are other effective products approved for the treatment of advanced renal cell cancer.

Appendix A (Key Information on Deaths Associated with or Related to Hepatic Failure)

Subject 121 (HYT109091): A 37 year-old female with advanced sarcoma who had no hepatic metastasis and normal hepatic function at enrollment received daily pazopanib (800 mg) plus topotecan on days 1 and 15 only. On Day 33 pazopanib was discontinued due to fatigue, anorexia, diarrhea, and transaminase elevations. On Day 36, she was admitted for similar symptoms and was found to have a Grade 4 ALT elevation. On day 40 she died of hepatic failure. Key laboratory and clinical information is listed below. The investigator considered the hepatic failure as possibly related to study drug, but not to concomitant medicines that included domperidone, oxazepam, loperamide, odansetron, and acetaminophen PRN. Hepatitis serology and other viral test results were negative. An autopsy showed hepatocellular necrosis and the hospital pathologist stated that this was consistent with drug-induced hepatic injury. The sponsor concluded that drug-induced liver injury cannot be ruled out in this case, but proposed that the injury may be due to ischemia. There was one recording of BP 115/80, HR 113 and Pox 99% 5 days after study initiation. The vital signs during hospitalization are shown below.

Date	Day 1	Day 15	Day 33	Day 36	Day 37	Day 39*
Vital signs	Not found (n/f)	n/f	T (n/f) BP 105/78 HR 109 RR (n/f) Pox 99%	n/f	T 37.5 BP 95/65 HR 103 RR (n/f) Pox 100% (O2 1L/min))	n/f
ALT (0-35 IU/L)	20	28	92	1934	2552	2800
T. bilirubin (3-21 µM)	11	9	16	n/f	43	43
Alkaline Phosphate (0-120 IU/L)	54	57	62	84	91	86
Creatinine (50-105 µM)	73	62	87	128	143	200
Acetaminophen (mg/L)	n/f	10.9	8.2	n/f	n/f	n/f

*On Day 39, PT was 47.9 (normal 11.5-14.5) and PTT 61 (normal 29-39)

FDA Assessment of Subject 121: This is a Hy's Law case, but the patient is not in the pazopanib monotherapy population. The hepatic injury and hepatic failure-related death were considered probably related to pazopanib and this is supported by the pathological evidence. The attribution of hepatic failure to topotecan and acetaminophen was considered unlikely because the last dose of topotecan was 18 days previously and because the serum acetaminophen levels were very low (A level below 15 mg/L at any time within 24 hours after ingestion is very unlikely to be associated with hepatotoxicity, Harrison's Principles of Internal Medicine, 16th Edition, 2005**).**

Subject 386 (VEG105192): A 60 year-old male with RCC metastatic to the lungs (no hepatic metastasis) and with normal liver function at baseline started pazopanib on Oct 19, 2006. He complained of severe nausea and sleepiness on Nov. 14, 2006 and was admitted on with shortness of breath. Physical examination showed hepatosplenomegaly on admission. Pazopanib was discontinued on due to an elevation in bilirubin. The patient died on . No autopsy was performed. Relevant lab and vital signs are listed below. The patient did not have a history of Gilbert's disease or hyperbilirubinemia. The investigator considered the hepatic injury as possibly related to pazopanib and ascribed the death as due to disease progression in the lungs. GSK concluded that the hepatic injury was related to liver ischemia as a terminal event secondary to respiratory and cardiac compromise.

Date					
Vital sign	T 36.5 BP 106/60 HR 105 RR (n/f)	T 37.0 BP 128/96 HR 103 RR (n/f)	T (n/a) BP 128/105 HR 126 RR 16 Pox 94% (RA)	T 37.0 BP 110/60 HR 98 RR (n/f) Pox 94% (RA)	Not found (n/f)
T. bilirubin (5-17 uM) [D bili<10]	11 n/a	30 n/a	40 [9]	n/f	62 [17]
ALT (12-41 IU/L)	12	19	15	n/f	1517
Alkaline Phosphate (44-132 IU/L)	141	124	116	n/f	147
Albumin (g/L)	31	29	27	n/f	24
Hemoglobin (g/dL)	11.9	13.7	13.2	n/f	11.9

*AST and LDH were not reported on that day.
The report of the CXR stated that there were extensive pulmonary metastasis, with signs of edema in the lungs.

FDA Assessment of Subject 386: Attribution of the hepatic injury and death to pazopanib can not be ruled out. (Note this patient was not included in the list of patients with fatal SAEs, but rather in the list of patients who died due to disease progression.)

Subject # (Study)	Brief History	LFT (Day)	Confounding Factors	Investigator's and Applicant's Assessment
Subject 233 **(VEG102616)**	71 year-old female with **normal hepatic function** and **no liver metastasis** at baseline (KPS 80%) developed hyperbilirubinemia 9 days after pazopanib was initiated. She was hospitalized on day 9 (BP 120/80 mmHg-HR 80) and died on day 13 "*due to hepatic insufficiency with multiorgan failure"*. No autopsy was performed.	ALT[1] 17 (baseline) **24 (day 9)** 1086 (day 12) Bilirubin[2] total/direct 0.5/0.1 (baseline) **2.3/0.5 (day 9)** nf /2.5 (day12) Alk Phos[3] 62 (baseline) **109 (day 9)** 182 (day 12)	Large tumor at right kidney (97x67); peritoneal carcinomatosis; pulmonary metastases; Co-med: acetaminophen Morphine UGT1A1 genotype: TA6TA7 (associated with decreased expression of UGT1A1)	There was no reasonable possibility that the hepatic failure and death were related to study drug, but rather to terminal disease progression and liver ischemia.
FDA Assessment of Subject 233: Attribution of the hepatic injury and death to pazopanib can not be ruled out given the acute clinical course. It is unclear whether the patient may have developed hepatic ischemia since no vital signs were found in her medical records during hospitalization.				

[1]Normal ALT < 33 IU/L
[2]Normal total bilirubin < 1.2 mg/dl; normal direct bilirubin < 0.2 mg/dL
[3]Normal alkaline phosphatase < 94 IU/L

Appendix B (Illustrative Examples of Severe Hepatoxicity: Adopted from Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation (drafted in October, 2007, and finalized in July, 2009)

Duract (bromfenac)

Bromfenac was a nonsteroidal anti-inflammatory drug (NSAID) studied for both short-term analgesia and long-term arthritis treatment. There was little evidence of hepatotoxicity in the short-term analgesic trials, but during longer term clinical trials in arthritis, ALT elevations >3xULN were seen in 2.8 percent of patients on bromfenac, compared to none in placebo group. Among 1,195 exposed patients, there were two cases in which there was elevated TBL as well as AT elevation in the clinical trial data submitted for review in the NDA. Concerns about possible liver toxicity led to the approval of bromfenac in July 1997 for short-term use only and not for osteoarthritis or rheumatoid arthritis. As an NSAID, however, it was prescribed long-term off-label in arthritic patients, and severe hepatotoxicity emerged. Within 6 months of approval, reports of severe hepatic failure, including two cases requiring liver transplant, were received. All severe cases involved the use of bromfenac for more than 10 days, the maximum duration of treatment recommended in the labeling.

In response, the FDA and the manufacturer strengthened the warnings in the package insert with a boxed warning, and issued a Dear Health Care Professional Letter. Despite these efforts, the manufacturer and the FDA continued to receive reports of severe injuries, including reports of death or need for liver transplantation (Moses and Schroeder et al. 1999; Hunter and Johnston et al. 1999; Rabkin and Smith et al. 1999; Fontana and McCashland et al. 1999). Given the availability of other effective NSAIDs, bromfenac was withdrawn from the market in June 1998. The two Hy's Law cases in the long-term-exposed population of about 1,000 subjects during drug development predicted an occurrence of severe hepatotoxicity during chronic use at a rate of about 1/5,000 to 10,000 people. Following approval, rates of acute liver failure for bromfenac were estimated to be in the range of 1/10,000 (Goldkind and Laine 2006).

Rezulin (troglitazone)

Troglitazone was approved by the FDA in January 1997 for the treatment of Type 2 diabetes mellitus. In reviews of the clinical trials of troglitazone conducted before approval there were no cases of liver failure among 2,510 subjects exposed to the drug in the NDA database, but 1.9 percent of troglitazone-treated subjects had ALT >3xULN compared to 0.3 percent of placebo-treated subjects, 1.7 percent had ALT >5xULN, and 0.2 percent (5 subjects) had ALT >30xULN (2 subjects in the last group also experienced jaundice). The median duration of troglitazone therapy before peak ALT elevation was 121 days. In the Diabetes Prevention Trial at the National Institutes of Health (NIH) performed after approval, 4.3 percent of 585 troglitazone-treated subjects had ALT ≥3xULN, 1.5 percent had ALT >8xULN, and 2 subjects had ALT >30xULN, compared to 3.6 percent of subjects with ALT ≥3xULN in the placebo group (Knowler and Hamman et al. 2005). One of the subjects in the Diabetes Prevention Trial with ALT >30xULN developed liver failure and died, despite receiving a liver transplant. The

second subject recovered. These data suggest that the rate of severe liver injury would be about 1 in 3,000 to 10,000.

After marketing, there were numerous reports of acute liver failure associated with troglitazone use (Gitlin and Julie et al. 1998; Vella and deGroen et al. 1998; Herrine and Choudary 1999), and four letters were sent to practicing physicians between 1997 and 1999, urging monthly monitoring and careful use. These letters did not significantly affect the monitoring done by physicians, and AT monitoring recommended in the Dear Health Care Professional Letters and in the package insert was not regularly performed (Graham and Drinkard et al. 2001). Moreover, an analysis of 94 cases of liver failure reported spontaneously to the FDA showed that the progression from normal hepatic test results to irreversible liver injury occurred in less than a month (the recommended monitoring interval) in 19 patients. The onset of injury began after 3 days to more than 2 years of troglitazone use (Graham and Green et al. 2003; Graham and Drinkard et al. 2003). Time from jaundice to hepatic encephalopathy, liver transplantation, or death usually was rapid, averaging 24 days. Troglitazone was withdrawn from the U.S. market in March 2000, when other drugs in the same class with similar efficacy but little or no evidence of hepatotoxicity became available (i.e., rosiglitazone, pioglitazone).

Apart from constituting another example of the predictive value of evidence of hepatocellular injury accompanied by even two cases of elevated bilirubin, there were other lessons learned from the troglitazone experience: 1) monitoring recommendations may not be well followed by physicians, even after warning letters are sent to all practicing physicians; and 2) some cases of severe hepatotoxicity occur rapidly, within less than a reasonable and practical recommended interval for monitoring, indicating that monitoring would provide at best only partial protection, even if recommendations were followed.

Exanta (ximelagatran)

Exanta (ximelagatran), an oral anticoagulant (antithrombin), was not marketed in the United States because of hepatotoxicity and other concerns discovered during clinical trials. Issues related to potential liver toxicity of ximelagatran were presented and discussed at an FDA advisory committee meeting in September 2004 (He 2004). During short-term clinical trials of the drug for prevention of thromboembolic complications after joint replacement surgical procedures, there was no increased rate of transaminase elevations in the ximelagatran group compared to the enoxaparin-warfarin group, and no serious hepatotoxicity was seen. But in longer term trials (more than 35 days) in patients with chronic atrial fibrillation to prevent embolic or thrombotic strokes, an increase in ALT >3xULN occurred in 7.6 percent of 6,948 patients compared to 1.1 percent of patients receiving warfarin treatment; and 1.5 percent of ximelagatran-treated patients had ALT >10xULN.

Increases in AT typically occurred 1 to 6 months after the initiation of ximelagatran administration with peak levels within 2 to 3 months postrandomization. Among the 531 ximelagatran patients with ALT >3xULN, 39 percent completed the trial on treatment,

while 61 percent discontinued the drug. Almost all patients with ALT >3xULN returned to <2xULN whether the drug was stopped or not, although the return to normal was faster if ximelagatran was stopped. Of 18 patients who resumed drug after ALT returned to normal, only 2 had elevations recur. Concomitant elevations of ALT >3xULN and bilirubin >2xULN were observed in 37 of about 7,000 patients with ximelagatran and 5 of 6,230 patients with comparator. At least 13 of 37 patients in the ximelagatran group had no alternative explanation for the concomitant ALT and bilirubin elevation. Nine of the 37 patients died, but in most cases the deaths were not clearly hepatotoxicity-related. Only one autopsy was done and it showed a small, friable and diffusely mottled liver suggestive of severe diffuse hepatic necrosis, but liver failure from ximelagatran might have contributed to some of the other deaths (He 2004; Lewis 2006; Kaplowitz 2006; Senior 2006; Temple 2006). Because severe hepatotoxicity was observed in an orthopedic surgery trial in an extended treatment of 35 days, Exanta was withdrawn in February 2006 from the 22 countries in which it had been approved, and further development in the United States was abandoned.

Again, short-term tolerance of ximelagatran, with resolution of even substantial elevations of ALT in most cases, did not predict long-term safety. The relatively high rate of Hy's Law cases, about 0.2 percent or 1/500 (13 cases among 7,000 exposed patients), predicted the occurrence of severe hepatotoxicity, at a rate of about 1/5,000 (10 percent of the rate of Hy's Law cases). In fact, at least one death occurred among the 7,000 exposed patients from subsequent liver toxicity, further supporting such an estimate.